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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| EXAMINER | |
|---|---|
| ART UNIT | PAPER NUMBER |
| | 14 |

**DATE MAILED:**

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/543,771 | Applicant(s) CARULLI ET AL. |
|---|---|---|
| | Examiner Sumesh kaushal | Art Unit 1633 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *2-13,24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 14-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s) _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The applicant's response filed on 08/13/01 is acknowledged. The supplemental amendment filed on 11/21/01 is entered.

### *Election/Restrictions*

Applicant's election with traverse of Group-I (Claims 1 and 14,-23) in Paper No. 13 is acknowledged. The traversal is on the ground(s) that non-elected Groups II-IV substantially overlap as each group involves HBM protein (i.e. SEQ ID NO:4). The applicant further argues that there is no serious burden to examine all the claims. This is not found persuasive for the same reasons of record as set forth in the official action mailed on 06/20/01. The earlier office action cleary states that Group I and IV are distinct because the invention of Group I requires the use of HBM protein, whereas the invention of group IV requires the use of an antibody to HBM protein. Antibodies and proteins have different structure and functions and different modes of operation. Furthermore, the method of identifying a molecule that binds to HBM in-vitro (Group-II) is distinct from a method to identify a molecule that modulate bone development in a host having a *high bone mass* or *low bone mass* phenotype in vivo (Group-III), because these methods have they have different modes of operation, different functions, or different effects. In addition, Group I and IV are distinct from Group II and III because they have different modes of operation, different functions, or different effects. For example, the binding of an antibody to HBM is distinct from the binding of ApoE to HBM due inherent structural and functional differences between antibody and ApoE. Furthermore, identification of a protein that modulate bone development in a host having a high bone mass or low bone mass phenotype requires quantitative analysis of host samples on 2D protein gels, which is distinct from above methods. Thus these inventions are distinct and are of separate use. The requirement is still deemed proper and is therefore made FINAL.

Claims 2-13 and 24-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

***Claim Rejections - 35 USC § 101 & 35 USC § 112***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 14-23 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility.

Claims 1 and 14-23 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The instant claims are drawn to an isolated amino acid sequences of SEQ ID NO:4. The claims are further drawn to a method of a of altering bone development in host comprising administering the amino acid of SEQ ID NO:4 to a Somatic cell and/or Germ-line cell of a host suffering from a bone development disorder. In addition the claims are drawn to a method of treating osteoporosis comprising administering the i) amino acid of SEQ ID NO:4 , ii) the extracellular domain of the amino acid of SEQ ID NO:4 and iii) intracellular domain of the amino acid of SEQ ID NO: 4.

The specification teaches that the nucleic acid sequences encoding the High Bone Mass (HBM) protein of SEQ ID NO:4 are allelic variants of Zmax1 gene. The specification further teaches that protein encoded by HBM (mutated) gene causes elevated bone mass while the protein encoded by Zmax1 (wild type) gene does not (spec. page 17, line 7-14). The specification further teaches Zmax1 gene is common in human population, while HBM gene is rare (spec. page 17 line 15-20). In addition, the specification disclosed the pedigree of the individuals used in genetic linkage analysis and concluded that HBM is an inheritable trait (spec. page 22, line 17, fig-1, page 107, example-1, US 5691153, 1997).

The invention as claimed encompasses the alteration of bone development and/or the treatment of osteoporosis. However, the specification fails to provide any guidance regarding the role of amino acid of SEQ ID NO:4 in the bone development and/or osteoporosis. The art at the time of filing teaches that the development of bones is not only polygenic but is also affected by various growth factors, hormones, nutrient uptake and pathogens. The strength and integrity of bones depends on maintaining a delicate balance between bone resorption by osteoclasts and bone formation by osteoblasts. With aging or as a result of disease, this delicate balancing act becomes tipped in favor of osteoclasts so that bone resorption exceeds bone formation, rendering bones brittle and prone to fracture. (Radan et al, Science 289:1508-1514, 2000, abstract).

The osteoporosis is a multifactorial disorder characterized by low bone mass and micro architectural deterioration of bone structure. The incidence of osteoporosis is higher in women than in men and increases sharply after 50 yrs of age. Recent studies reveled that genetic factors plays an important role in the pathogenesis of osteoporosis and the segregation analysis reveled that bone mineral density is under polygenic control (Kundu et al, Peptides 20:523-537, 1999. page 523, col.1-2). The most common cause of osteoporosis in women is the decrease in estrogen that accompanies menopause. Estrogen loss is associated with elevated bone resorption caused by a rise in osteoclast number, which is driven by increases in the cytokines that regulate osteoclast generation (RANK-ligand, TNF-a, IL-1, IL-6, IL-11, M-CSF and prostaglandin E). Production of all of these cytokines is either directly or indirectly suppressed or regulated by estrogen (Rodan, page 1509, col.1, para. 3).

Several hormones regulate the bone mineralization and demineralization, primarily by parathyroid hormone (PTH). The higher concentration of PTH inhibits the bone formation whereas the low serum concentration increases the bone mass (Kundu et al page 524, col. 2, sec. 4 1; Ziegler et al, Steroids 63:344-348, 1998, page 345, fig-1). Furthermore, bone formation is also affected by nutrient uptake. The reduced caloric intake is associated with reduced calcium intake which results in decrease in bone mass over time (Bollag et al, Endocrinology, 141(3)1228-35, 2000, page 1234, col.1 para.2).

Considering the multifactorial nature of bone development and osteoporosis, the specification fails to teach effect of HBM protein (SEQ ID NO:4) on osteoblast or osteoclast activity. In addition, the specification fails to teach that HBM-protein (as claimed) modulates a hormone like PTH that regulates bone development.

Furthermore, the official sequence search reveled that the amino acid sequences of SEQ ID NO:4 matches 99.6% to the amino acid sequence of a Low Density Lipoprotein Receptor Related Protein (LRP5) expressed in hepatocytes and adrenal cortex and is know to play a key role in the hepatic clearance of cholesterol carrying LDL (Kim et al, J Biochem. (Tokyo) 124:1072-1076, 1998, page 1072, col.1). Considering the high amino acid sequence homology (99.6%) one skill in the art would conclude that the amino acid sequence of SEQ ID NO:4 falls in the realm of LDL-receptor-related-protein family that would regulate hepatic clearance of cholesterol carrying LDL. Since the specification fails disclose a single working example that teaches the polypeptides of SEQ ID NO:4 regulates bone formation, it is unclear how one skill in the art would use the SEQ ID NO:4 to alter bone development and/or osteoporosis.

In addition the invention as claimed is drawn to a method wherein the amino acid sequences of SEQ ID NO:4 is administered to a somatic and/or a germ-line cell. It is unclear how the administration of the polypeptide (as claimed) into somatic and/or a germ-line cell would later bone development and or treat osteoporosis. The state of art at the time of filing

teaches that proteins or drugs that modulates bone development and/or osteoporosis are administered systemically into patients to initiate the cascade of bone formation.

The specification fails to disclose that whether the high bone mass (HBM) phenotype is the result of the loss of Zmax1 protein activity or is the result of altered Zmax1 protein function due to the HBM mutation. The polypeptide as claimed appears to be a receptor comprising extracelluar and interacelluar domains. It is unclear how one skill in the art would purify the receptor (as claimed) in an active and soluble form, which upon administration to a subject would not loose its specific activity due to in vivo degradation. Similarly, it is unclear how one skill in the art would use the polypeptide wherein the interacellular domain is involved in a signal transduction mechanism. The specification fails disclose the role of polypeptide as claimed in any signal transduction pathway, which leads to bone development. Furthermore, it is unclear what is the target tissue for the polypeptide as claimed. It is even unclear whether the polypeptide activates osteoblast/osteoclast activity or modulates a hormone like PTH, which regulates bone development.

The specification teaches that Zmax1 and HBM differs by a mutation at position 582, which falls in the extra-cellular domain of the polypeptide as claimed (spec. page 17 line 15-20). The specification fails to teach the targeted delivery of HBM polypeptide to a cell involved in the bone development. It is unclear how one skill in the art would specifically target the membrane of bone cells so that the administered HBM-receptor takes over the Zmax1 function by altering interacellular signal transduction in vivo. Furthermore, it is unclear how the administration of intercellular domain in vivo would modify the interacellular signal transduction of bone cells, which result in HBM phenotype. Furthermore, the administration of extracellular domain alone would be non-productive as it only completes with a natural ligand for HBM receptor protein. The specification fails to disclose a natural ligand for the extracellular domain of HBM-receptor protein, blocking of which regulates the bone formation. At best the only know ligand for the for the SEQ ID NO: 4 would be LDL (see Kim et al) and it is unclear how one skill in the art would regulate bone development and or osteoporosis by blocking LDL activity.

Thus in considering the state of art and the guidance provided in the specification, it is unclear how one skilled in the art would use the invention as claimed to alter bone development and/or the treat the osteoporosis. One would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The amount of experimentation required would include administration of the amino acid sequence of SEQ ID NO:4, extracellular domain of SEQ ID NO:4 and intracellular domain of SEQ ID NO:4 into patients suffering from any and all bone defects (Osteoporosis, Paget disease, Bone cancer, Inflammatory bone disease etc) and the evaluation of bone development.

The invention as claimed does not have a credible asserted utility or a well establish utility because the specification fails to disclose that whether the HBM phenotype is the result of the loss of Zmax1 protein activity or is the result of altered Zmax1 protein function due to a mutation in Zmax1 gene. The specification fails to disclose a specific function of HBM protein in the development of HBM phenotype. The art a the time of filing clearly indicate that SEQ ID NO:4 falls in the realm of LDL-receptor-related-protein family that would regulate hepatic clearance of cholesterol carrying LDL. Since the specification fails disclose a single working example that teaches the polypeptides of SEQ ID NO:4 regulates bone formation, it is unclear how one skill in the art would use the SEQ ID NO:4 to alter bone development and/or osteoporosis. Therefore, the asserted use for the claimed amino acid sequences is not supported by either a credible or well-established utility, since no function can be ascribed to the polypeptide as claimed. The only immediate apparent utility for the instant invention would be its further scientific characterization of the claimed polypeptide in the bone development and/or osteoporosis

***Claim Objections***

Claims 20-23 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel

the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The method of using exteracellular and interacellular domains as claimed in claims 20 and 22 does not further limits the amino acid sequences of SEQ ID NO: 4, recited in claim 1. Rewriting claims 20and 22 in independent form would obviate this rejection.

***Conclusion***

Claims 1 and 14-23 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377. If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED to facilitate further examination.

**SUMESH KAUSHAL**
**PATENT EXAMINER**

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER